UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/637,650	08/11/2000	Chao-Feng Zheng	25436/1510	7825

27495 7590 07/17/2003

PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS / STR
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER
MCKELVEY, TERRY ALAN

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 07/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/637,650	Applicant(s) ZHENG, CHAO-FENG	
	Examiner Terry A. McKelvey	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 June 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): objections to claims 33-38.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheets.*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-9 and 24-26*.

   Claim(s) withdrawn from consideration: *10-23 and 27-32*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *See Continuation Sheets.*

Terry A McKelvey

TERRY MCKELVEY
PRIMARY EXAMINER

Continuation Sheets

Continuation of 5. The applicant argues again that Montminy teaches the use of three constructs and the instant invention contains two elements. This argument was specifically addressed in the Response to Arguments section, pages 3-4, of the Final Rejection mailed 3/7/03. The system taught by Montminy reads on the claimed system for the reasons previously discussed. The applicant did not respond to the arguments previously presented in that Action and thus repeating the same argument without addressing the previous comments concerning this argument is not persuasive in overcoming the rejection of record.

Also, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., having only a two element assay system) are not recited in the rejected claim(s) because although two elements are recited in the claims, the use of "comprising" opens the claims to having additional elements, including a third element. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The applicant argues that the Examiner has mischaracterized Gilman et al and that the Examiner recites two passages out of context, in an unsuccessful attempt to show that the Gilman et al reference teaches stable integration of the "entire assay system taught by Montminy" (citing this phrase from the first Office Action, paragraph bridging pages 5-6).

First, the applicant has mischaracterized the statement in the first Office Action. Here is the entire statement: "One would have been motivated to do so for the expected benefit of being able to integrate the construct at a particular locus as taught by Gilman et al, which is useful in making cell lines which have the entire assay system taught by Montminy, with a known number of copies of each component of the system, which gives one of ordinary skill better control and reproducibility of the system." This is the motivation statement for the rejection. It is a statement of why one of ordinary skill in the art would have been motivated to make the substitution or change described in the paragraph above in the rejection (i.e., stably integrate the Montminy assay system), based upon the teachings of the cited references and what is known to one of ordinary skill in the art. The reference to what Gilman et al teach is in the first part of the sentence "expected benefit of being able to integrate the construct at a particular locus as

taught by Gilman et al". It is not an allegation that the Gilman et al reference directly teaches stable integration of the "entire assay system taught by Montminy". The part of the sentence that refers to the "entire assay system taught by Montminy" essentially asserts that one of ordinary skill in the art, given the teachings of Gilman et al of stable integration of a heterologous transactivated gene expression system (an expression system based upon expression of a heterologous transcription factor and having a target gene that has a recognition site for the transcription factor, so that the target gene expression is transactivated by the transcription factor), would have been motivated to apply the teachings of stable integration to another heterologous transactivated gene expression system, such as the whole assay system taught by Montminy (which is another heterologous transactivated gene expression system), for the reasons stated, (to produce cell lines with) a known number of copies of each component of the system, which gives one of ordinary skill better control and reproducibility of the system.

Second, concerning the applicant's allegation that the Examiner mischaracterized the Gilman et al reference, the applicant's argument is not persuasive. The applicant is essentially arguing that Gilman et al teach that the chimeric

constructs may be introduced into a host cell by any convenient means, including teaching a list of the general means of doing so in the art and that rather than "teach" stable integration, the cited reference teaches that any conventional means for achieving heterologous gene expression, whether transient or stable, can be used to introduce the chimeric construct comprising a transcription factor and a target gene. The applicant seems to be suggesting that because several alternative approaches are taught (the different ways that the constructs can be placed into cells) that it is a mischaracterization of the reference to indicate that it teaches one of the approaches (stable integration). This argument is completely without merit because the reference, by teaching that any convenient means can be used, followed by a listing of the different convenient means, which clearly includes stable integration because it is specifically stated, is teaching one of ordinary skill in the art various approaches and that any of them can be used. Thus, it is not a mischaracterization of Gilman et al to indicate that it teaches stable integration of the expression constructs because it clearly does, in addition to other ways such as transient transformation of the constructs. It is simply not persuasive to suggest that when a reference teaches several approaches of doing something,

including reciting a particular approach, that it does not teach that particular approach. The reference clearly intends that all of the recited approaches be taught, not none of them.

The applicant argues that: "The Examiner continues to mischaracterize the teachings of the Gilman et al reference by immediately following the first misstatement with a second out-of-context reference, this time to a reporter gene construct in column 13. The Examiner seems to be implying that the Gilman references teaches stable integration of a construct comprising a transcription factor and a reporter gene. However, the Examiner has failed to point out that the passage in column 13 relates to transient expression of a construct comprising a reporter gene and a binding site for the transcription factor using an expression vector (plasmid). The purpose of using the reporter gene is to determine the activity of the transcription factor, i.e., whether it is positive or negative regulator of transcription."

The applicant's arguments are without merit. Like the earlier arguments, the applicant mischaracterizes this part of the rejection of record also. The only references to column 13 in the rejection are: "Reporter systems for assaying the fusion protein transcriptional activity in the cell are also taught which comprises a reporter gene such as luciferase, CAT,

secreted alkaline phosphatase, etc, operatively linked to a binding site for the transcription factor (column 13). Gilman et al also teach that the transcription factor can be expressed in a cell-specific manner by operatively linking the gene encoding the factor to a cell-specific promoter (column 13) and/or in a constitutive manner (columns 23-24)." This part of the rejection is not used to imply that the reference teaches stable integration of a construct comprising a transcription factor and a reporter gene, but instead to show that Gilman et al teach what is actually stated. This section was not relied upon for teaching of stable integration, but instead to show that a reporter gene operatively linked to the recognition site was taught by the reference as a target gene (and particular reporter genes are specifically taught, used to address some dependent claim limitations drawn to particular marker genes), and that the reporter constructs are taught for assaying the transcriptional activity of the transcription factor in the cell (which is what constructs of this type are used to measure, including the construct which is a part of the claimed invention). The other teachings of Gilman et al, described above, are relied upon for the teachings of stable integration of the constructs encoding the transcription factor and target gene construct which is the target gene operatively linked to

the recognition site for the transcription factor. The fact that the reporter construct teachings follow the stable integration teachings in the rejection is simply due to the fact that the teachings relied upon are being set forth in the rejection and, because Office Action writing is a linear format, one must precede the other.

Additionally, actually the Gilman et al reference DOES teach stable integration of a construct comprising a transcription factor and a reporter gene (which is the target gene): at column 18, line 36 to column 19, line 29. Gilman et al teach an assay system comprising an expression vector directing the production of the transcription factor (indicated as 1(a)) and (2) a reporter plasmid directing the expression of a reporter gene, preferably identical in design to the target gene described above (i.e., multiple binding sites for the DNA-binding domain, a minimal promoter element, and a gene body) but encoding any conveniently measured protein (column 18, lines 40-43 and 49-54). The reference then goes on to describe the constructs in a transient assay (column 18, line 55 to column 19, line 10). This is followed by teaching the preferred use of the constructs stably integrated into the cell (column 19, lines 11-29): "The transient transfection assay is not an extremely stringent test in most cases, because the high concentrations of

plasmid DNA in the transfected cells lead to unusually high concentrations of the DNA-binding protein and its recognition site, allowing functional recognition even with relatively low affinity interactions. A more stringent test of the system is transfection that results in the integration of the introduced DNAs at near single-copy. Thus, both the protein concentration and the ratio of specific to non-specific DNA sites would be very low; only very high affinity interactions would be expected to be productive. This scenario is most readily achieved by stable transfection in which the plasmids are transfected together with another DNA encoding an unrelated selectable marker (e.g., G418 resistance). Transfected cell clones selected for drug resistance typically contain copy numbers of the nonselected plasmids ranging from zero to a few dozen. A set of clones covering that range of copy numbers can be used to obtain a reasonably clear estimate of the efficiency of the system." So, whether or not it is implied that Gilman et al teaches stable integration of a construct comprising a transcription factor and a reporter gene is moot because the reference actually does teach it.

The applicant argues that there is no suggestion in the cited references to combine their teachings to stably integrate a recombinant DNA construct into a cell, as required by

Applicant's claims. The applicant goes on to argue that there is no teaching or suggestion of integrating a reporter gene construct into the genome of a host cell and in fact such integration would destroy the intended purpose or function of the Gilman et al invention, which is to provide methods and materials (recombinant DNA sequences and cells comprising those sequences) for achieving high-level expression of a target gene in genetically engineered cells, including genetically engineered cells within whole organisms. It is argued by the applicant that the only disclosed use of a reporter gene in the Gilman et al reference is to test the activity of the transcription factor, which is then incorporated into a host cell, and to stably integrate a reporter gene into these cells or organisms would serve no purpose, and would likely negatively impact the expression level of the target gene, as well as the function and viability of the modified cell.

These arguments are not persuasive for the following reasons. The teaching or suggestion for integration of a reporter gene construct into the genome of a host cell comes from several parts of the teachings. As described above and in the rejection, Gilman et al teaches that the target gene construct (and the transcription factor construct) can be stably integrated into the cell. This reference also teaches that the

target gene construct can be a reporter gene construct, used to assay the transcription ability of the transcription factor. Thus, to one of ordinary skill in the art, Gilman et al teaches that the target gene construct (which can be a reporter gene construct, used to assay the transcription ability of the transcription factor) can be stably integrated into the cell. Also, as described above, Gilman et al actually does specifically teach stable integration of a construct comprising a transcription factor and a reporter gene into a cell. Despite what the applicant argues, integrating a reporter gene construct into the genome of a host cell does not destroy the intended purpose or function of the Gilman et al invention because Gilman et al actually teaches doing so generally for target gene constructs and when the target gene constructs are specifically reporter gene constructs for testing the function of the transcription factor by use of the integrated reporter construct. Why would Gilman et al specifically teach stable integration of the constructs if integration destroyed the intended purpose or function of their invention? The applicant's argument concerning integration destroying the intended purpose or function of the Gilman et al invention seems to be based upon a mischaracterization of the rejection of record. The rejection is not based upon the obviousness of

stably integrating a reporter gene construct in addition to the target gene construct in cells taught by Gilman et al. Instead, it is actually based upon the obviousness of the combination of the teachings of Montminy in view of Gilman et al. The rejection is based upon the obviousness of applying the teachings of Gilman et al regarding stably integrating constructs encoding a transcription factor gene and a target gene which is operatively linked to a recognition site for the transcription factor, including specifically when the target gene is a reporter gene, to modify the analogous system of Montminy which also comprises constructs encoding a transcription factor gene and a target gene (which is a reporter gene) which is operatively to a recognition site for the transcription factor. The motivation to combine the teachings of the cited references was clearly stated in the rejection of record: "One [of ordinary skill in the art] would have been motivated to do so for the expected benefit of being able to integrate the construct at a particular locus as taught by Gilman et al, which is useful in making cell lines which have the entire assay system taught by Montminy, with a known number of copies of each component of the system, which gives one of ordinary skill better control and reproducibility of the system." This is the motivation that one of ordinary skill in

the art understands is a motivation for integrating expression constructs in cells, in place of merely transiently transfecting them into the cells. This motivation for stably integrating constructs comprising encoding a transcription factor and a reporter gene is also specifically addressed by Gilman et al (cited earlier): a more stringent test of the system (assaying for the transcription ability of the transcription factor) is (stable) transfection that results in the integration of the introduced DNAs at near single-copy, and that a set of clones covering the range of zero to a few dozen copy numbers can be used to obtain a reasonably clear estimate of the efficiency of the system. This is essentially the same motivation as cited in the rejection because making cells that have the constructs stably integrated results in cells having controlled and known copy numbers of the constructs which, for assays, results in better control and reproducibility of the system, i.e. allow more efficient measurement of the transcription caused by the transcription factor. That is, the ability of the assay to determine the transcription ability of the transcription factor by use of a reporter gene operatively linked to a recognition site for the transcription factor is more stringent and thus more efficient when the construct expressing the transcription factor and the reporter gene construct are stably integrated,

which, to one of ordinary skill in the art, is clearly usefully applied to the analogous assay system taught by Montminy because the Montminy assay system is also used to measure the transcription ability of the transcription factor by use of the same type of reporter gene construct. Thus, one of ordinary skill in the art would have been motivated to modify the teachings of Montminy by stably integrating the assay taught by Montminy, as taught by Gilman et al for an analogous system, for the expected benefit as described above and taught by Gilman et al.

Finally, the applicant argues that "... even if combined, the teachings of Montminy and Gilman et al do not result in the claimed invention. Neither Montminy nor Gilman et al. teach a stably integrated recombinant nucleic acid construct containing a report gene operably linked to a recognition sequence for a sequence-specific DNA-binding protein, and a sequence encoding a fusion protein, wherein the fusion protein comprises a sequence-specific binding domain and a conditionally active transactivation domain of CREB." This argument is essentially arguing that neither reference teaches the whole invention and seems to be arguing that thus, even if the teachings are combined, do not teach the claimed invention. In response to applicant's arguments against the references individually, one

cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). An argument that neither reference teaches the whole invention is not a persuasive argument that a combination of the teachings of the cited references fails to teach the claimed invention.

The Examiner respectfully submits that a prima facie case of obviousness of the claimed invention was made in the prior Office Actions and that the applicant's arguments of record in the prior Office Action and present in the instant reply to the final rejection are not persuasive in overcoming the corresponding rejection of record, and thus the rejection of all pending claims under 35 USC 103(a) is properly maintained.

Continuation of 10. Other: It is noted that the claims still recite "said fusion protein comprising a sequence-specific DNA binding domain ... and a conditionally active transactivation domain of CREB". As described in the rejections of record, this reads on the full length CREB (because CREB has that domain in its full length protein) fused to a Gal4 DNA binding domain taught by Montminy as a preferred embodiment at column 7, lines 5-7. If the applicant is interested in further

prosecution of the instant application, it is suggested that drafting the claims to no longer read on the full length CREB protein fused to Gal4 DNA binding domain by using "comprising ... an isolated conditionally active transactivation domain" or "consisting essentially of ... a conditionally active transactivation domain" whichever there is support for, or use of another limitation to exclude full length CREB/Gal4 DNA binding domain taught by Montminy would appear to overcome the rejections of record. However, it is noted that such a significant change of the claims would necessitate a further consideration and search that would only be entered upon filing of an RCE or in a continuation application.